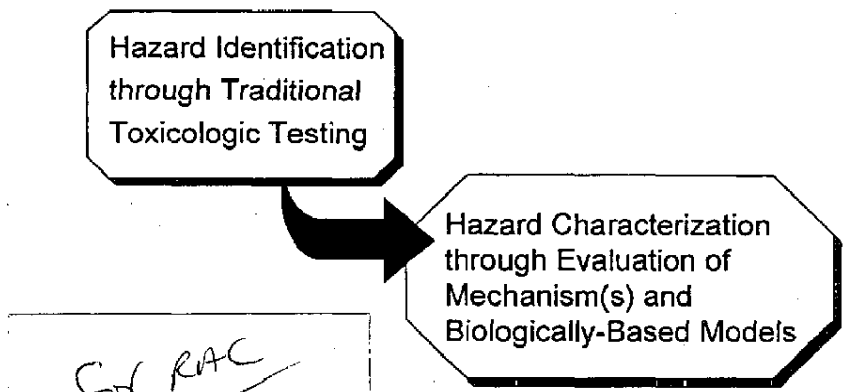
Evolution of Hazard Characterization



W Farland SOT 2000

for RAC
Solomon
2/28

Mechanism *vs.* Mode-of-Action

Mechanism of action:

Detailed molecular description of a key event in the induction of cancer or other health endpoints

Mode-of-Action:

Key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer or other health endpoints

W Farland SOT 2000

PM3006856878

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Mode-of-Action --

- How does the chemical produce its effect?
- Are there mechanistic data to support this hypothesis?
- Have other mechanistic hypotheses been considered and rejected?

W Farland SOT 2000

How is mode-of-action information used?

Address Uncertainty in Risk Assessment:

- Comparative Structure Activity Relationships (SAR)
- Relevance of animal data for extrapolation
- Shape of dose-response curve
  - → Range of Observation
  - → Range of Inference
- Susceptibility of individuals/ subpopulations

W Farland SOT 2000

PM3006856879

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Demonstrating a Mode-of-Action --

To show that a postulated ***mode-of-action*** is operative, it is generally necessary to:

- ? **outline** the sequence of events leading to effects;
- ? **identify** key events that can be measured; and
- ? **weigh** information to determine whether there is a causal relationship between events and cancer formation.

W Farland SOT 2000

Framework --

- Summary Description of Postulated Mode-of-Action
- Topics:
  1. *"Identify key events" (? BIOMARKERS?)*
  2. *"Strength, consistency, specificity of association"*
  3. *"Dose-response relationship"*
  4. *"Temporal relationship"*
  5. *"Biological plausibility and coherence"*
- Conclusion

W Farland SOT 2000

PM3006856880

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Key Event--

DEFINITION:

An empirically observable, precursor step that is a necessary element of the mode-of-action, or is a marker for such an element

W Farland SOT 2000

Key Event --

Examples:

- Metabolism
- Receptor-ligand changes
- DNA or chromosome effects
- Increased cell growth and organ weight
- Hormone or other physiological perturbations
- Hyperplasia, cellular proliferation

W Farland SOT 2000

PM3006856881

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Use of Mode-of-Action Information: *Examples*

■ Formaldehyde	⇨	DNA crosslinks
	⇨	Cell proliferation
■ Methylene Chloride	⇨	Pharmacokinetics
	⇨	Genetic polymorphisms
■ d-Limonene	⇨	alpha-2-u-globulin, etc.
■ Chloroform	⇨	Cytotoxicity
■ Dioxin ■ Phthalates	⇨	Receptor-mediated responses

W Farland SOT 2000

Use of Mode-of-Action Information: *More Examples*

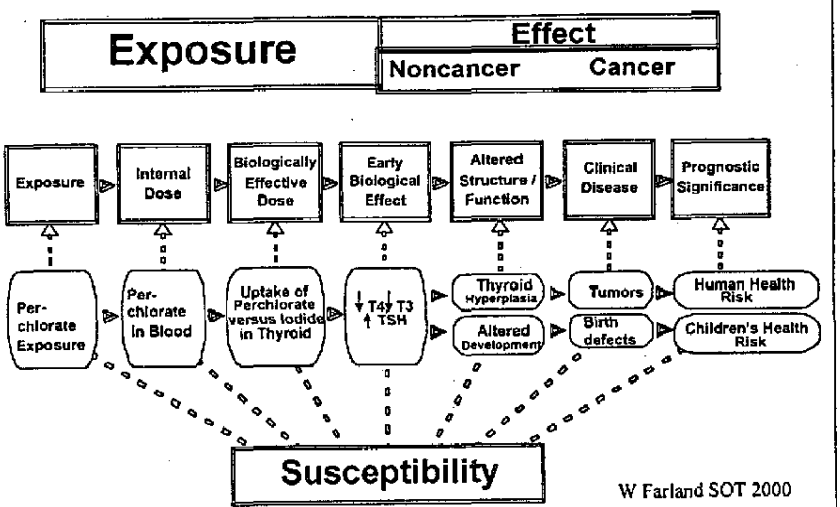
■ BaP	⇨	DNA reactive metabolites
	⇨	Cell proliferation
■ Amitrole	⇨	Increased Thyroid Stimulating Hormone (TSH)
	⇨	Cell proliferation
■ Melamine	⇨	Increased urinary pH
	⇨	Irritation
■ Vinyl Acetate	⇨	Cytotoxicity
	⇨	Cell proliferation
■ Perchlorate	⇨	Altered thyroid homeostasis

W Farland SOT 2000

PM3006856882

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Proposed Mode-of-Action Model for Risk Assessment of Perchlorate



Characteristics of Dose-Response

- Linear
- Sublinear
- Supralinear
- U-Shaped

W Farland SOT 2000

PM3006856883

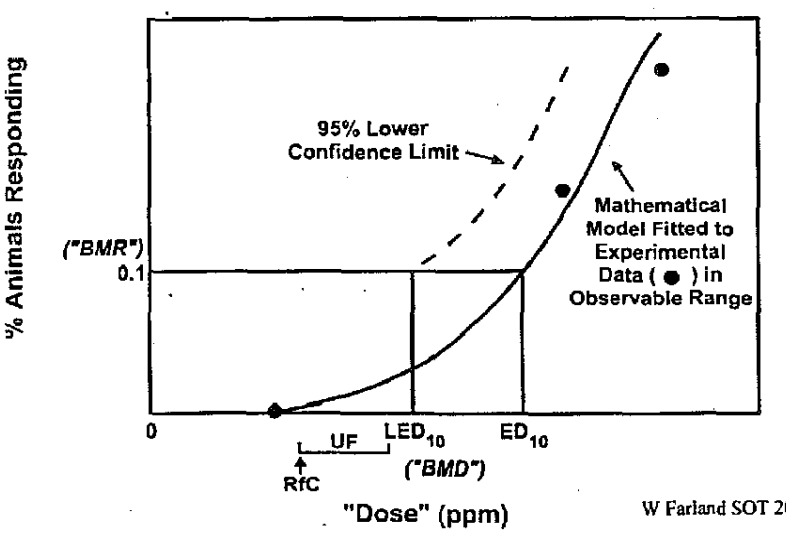
Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Comparison of Outputs of Dose-Response Analysis

- Probabilistic Estimate of Upper Bound on Risk
- Margin-of-Exposure (M-O-E)
- Reference Dose (RfD)
- Benchmark Dose (BMD)
- NOAEL/LOAEL

W Farland SOT 2000

"Benchmark Dose" Approach to Dose-Response Analysis for Noncancer Endpoints



W Farland SOT 2000

PM3006856884

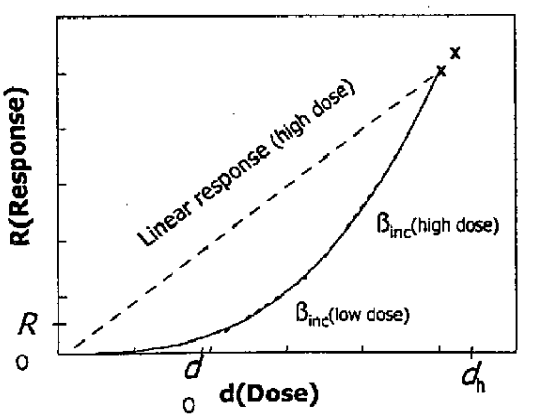
Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Use All Information to Design Cancer Dose-Response Assessment

- Tumor data
- Pharmacokinetics and metabolism data
- Data on effects of agent on carcinogenic processes

W Farland SOT 2000

Comparison of Slopes *



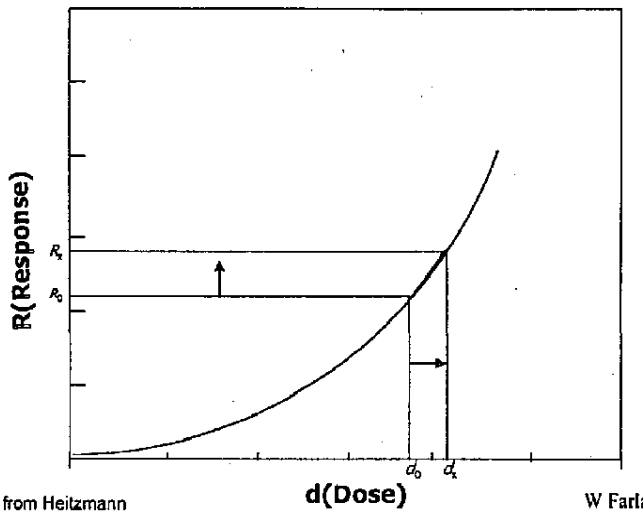
W Farland SOT 2000

* Adapted from Heitzmann and Wilson (1997)

PM3006856885

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Additivity to Background *



* Adapted from Heitzmann and Wilson (1997)

W Farland SOT 2000

Use of Mode of Action Data in Dose Response Assessment

- Construct a biologically-based or case specific model
- Link dose response curve for precursor effect to dose response for tumor effect
- Use dose response for other effect in lieu of that for tumor effect if it is judged to be a better measure of potential risk
- Use to inform assessment of possible dose response in range of extrapolation

W Farland SOT 2000

PM3006856886

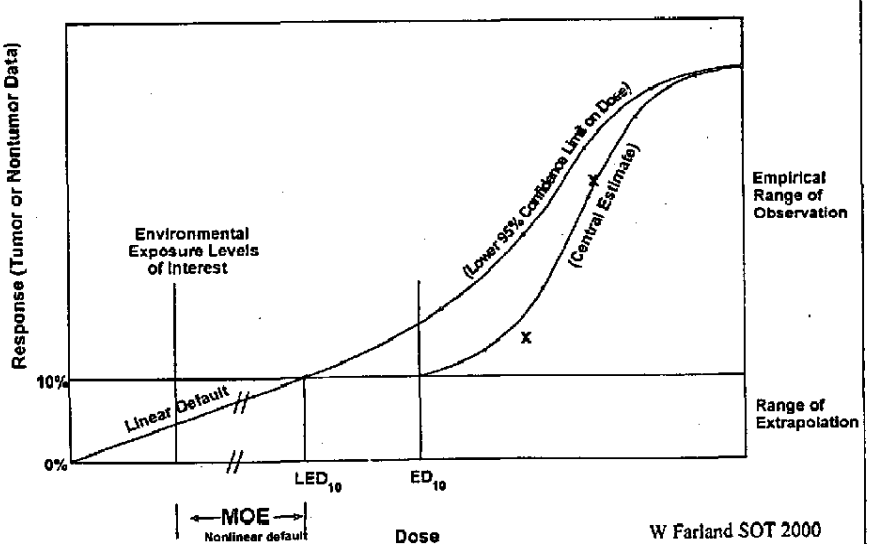
Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Two Step Dose Response Assessment

1. *First step*
   - Data in range of observation
2. *Second Step*
   - Evaluation in range of human exposure (Extrapolation)

W Farland SOT 2000

Dose Response Assessment



PM3006856887

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Dose Response Assessment -- *First Step, Range of Observation*

- *Use tumor data and other effect data*
  - Choose biologically based model if possible
  - Second choice is curve fitting
- *Explore lower range of observed data*
  - Identify benchmark dose for comparison with non-cancer effect assessments
  - Identify lowest reliable part of dose response curve ("point of departure" for extrapolation range)

W Farland SOT 2000

Dose Response Assessment-- *Second Step, Range of Human Exposure*

- *Use approach(es) indicated by mechanism of action*
  - Choose biologically based model if possible
  - Second choices are:
    - linear approach

      or
    - non-linear approach

      and/or
    - margin of exposure (**M-O-E**) analysis (how far is observed range from human exposure range?)
- *Characterize results, presenting alternative approaches when appropriate*

W Farland SOT 2000

PM3006856888

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Decision Logic for Dose Response Assessment

- *Linear*
  - DNA reactive or other evidence supporting linearity
  - not DNA reactive but insufficient data to characterize a non-linear mode of action
- *Non-linear*
  - not DNA reactive or otherwise linear, and sufficient data to characterize a non-linear mode of action
- *Both*
  - differing activity at different sites
  - complex activity needing both approaches to describe

W Farland SOT 2000

Where do we go from here?

- ☑ Development/validation of sensitive tools aimed at understanding mode-of-action
- ☑
- ☑ Incorporation of "Framework" Concept
- ☑
- ☑ More Attention to Route-Specific/ Situation-Specific Characterizations
- ☑
- ☑ Addressing Sensitive Subpopulations

"Biologically-Based Risk Assessments..."

W Farland SOT 2000

PM3006856889

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001

Biologically-Based Risk Assessment

- Refine estimates of dose to relevant targets through use of biomarkers of exposure
- Improve hazard characterization through use of biomarkers of response with mechanistic linkage to endpoints of concern
- Strengthen inferences regarding the shape of dose/response curves outside the range of observation
- Identify targets of opportunity for further study in potentially sensitive human populations

W Farland SOT 2000

Additional Reading

- International Life Sciences Institute (ILSI)(1995) The Use of Biological Data in Cancer Risk Assessment. In: Olin, S.;Farland,W.; Park, C.; Rhomberg, L.; Scheuplein, R.; Starr, T.;Wison, J., eds. Low-dose Extrapolation of Cancer Risks: Issues and Perspectives. Washington, DC: ILSI Press; pp. 45-60.
- NRC (1994) Science and Judgment in Risk Assessment. Committee on Risk Assessment of Hazardous Air Pollutants, Commission on Life Sciences, NRC. Washington, DC: National Academy Press.
- U.S. Environmental Protection Agency (1996) Proposed Guidelines for Carcinogen Risk Assessment. 61 Federal Register, pp. 17960-18011.

W Farland SOT 2000

PM3006856890

Source: https://www.industrydocuments.ucsf.edu/docs/nylx0001